Evidence-Based Systematic Review: Drug-Induced Hearing Loss—Amikacin

Tobi Frymark
Hillary Leech
Rob Mullen
Tracy Schooling
Rebecca Venediktov
Beverly Wang

National Center for Evidence-Based Practice in Communication Disorders,
American Speech-Language-Hearing Association, Rockville, MD

Introduction

Amikacin was first introduced in 1972 as a semisynthetic derivative of kanamycin A. One advantage of amikacin over other antibiotics is its resistance to inactivating enzymes, allowing it to be more active against pathogens resisted by other aminoglycosides (Siegenthaler, Bonetti, & Luthy, 1986). Amikacin use has been investigated in several populations, including neonates (Langhendries et al., 1993), febrile neutropenic patients (Axdorph, Laurell, & Björkholm, 1993), patients with pelvic inflammatory disease (Ibrahim et al., 1990), systemic infection (Maller et al., 1993), skin structure infections (Rodriguez-Noriega, Esparza-Ahumada, & Morfin-Otero, 1995), and acute pyelonephritis (Kafetzis et al., 2000). There is concern that widespread use of amikacin could lead to increased resistance of this drug (Philips & Cassady, 1982). Therefore, amikacin is often used as a reserve antibiotic. As with other aminoglycosides, adverse effects of nephrotoxicity, vestibulotoxicity, and cochleotoxicity are noted (Siegenthaler et al., 1986). According to a systematic review published in 1995, the pooled incidence of ototoxicity in amikacin users was 5.4% (range: 1.2% –

20%). There was no pooled difference in ototoxicity incidence between once- and multiple-daily dosing (Blaser & König, 1995).

This systematic review is intended to inform audiologists regarding the potential effects of amikacin administration on hearing loss. Specifically, the review addresses the incidence and persistence of amikacin-related hearing loss and the effects of dosage, route of administration, schedule of administration, and concurrent ototoxic drug use on hearing. Audiologists may use this information to make administration suggestions to physicians, determine appropriate audiological monitoring schedules, and provide optimal hearing treatment as necessary to reduce the risk or impact of hearing loss.

This systematic review is one of a series of systematic reviews addressing the effects of aminoglycoside use on hearing function. Two other systematic reviews that address gentamicin-induced hearing loss and tobramycin-induced hearing loss are included in the series. Additional information pertaining to the objectives of these systematic reviews and procedures for searching, sifting, and appraising the evidence is included in the introductory paper titled Evidence-Based Systematic Review (EBSR): Drug-Induced Hearing Loss—Aminoglycosides.

The six clinical questions specific to this review are as follows:

1. What is the likelihood of persons treated with amikacin developing hearing loss?
2. What is the persistence of hearing loss in persons treated with amikacin?
3. Is the likelihood of amikacin-induced hearing loss affected by dosage?
4. Is the likelihood of amikacin-induced hearing loss affected by route of administration?
5. Is the likelihood of amikacin-related hearing loss affected by schedule of administration?
6. Is there evidence of a synergistic effect on hearing loss if multiple ototoxic drugs (e.g., aminoglycosides, antineoplastics, etc.) are taken concomitantly with amikacin?

Results

Fifteen studies were identified for inclusion in this review. The studies provided data to address one or more of the clinical questions under review (see Table 1). The majority reported data on the incidence of hearing loss following amikacin treatment (Question 1). Several studies provided information to determine the incidence of hearing loss by amikacin dosage (Question 3), route of administration (Question 4), and schedule of administration (Question 5). Only three studies examined the persistence of hearing loss (Question 2), and two examined the synergistic effect on hearing of amikacin paired with other potentially ototoxic drugs (Question 6).

Table 1. Included studies and corresponding clinical questions addressed.

Study	Question 1	Question 2	Question 3	Question 4	Question 5	Question 6
Axdorph et al., 1993	X	X	X		X	X
Blum, 1995	X		X	X	X	
The International Antimicrobial Therapy Cooperative Group, 1993[a]	X		X	X	X	
Charnas et al., 1997	X		X	X	X	
de Jager & van Altena, 2002	X			X		X
Fausti et al., 1999	X					
Forsyth et al., 1997		X	X	X	X	
Giamarellou et al., 1991	X		X	X	X	
Ibrahim et al., 1990	X		X	X	X	
Kotze et al., 1999	X	X	X	X		
Langhendries et al., 1993			X	X	X	
Maller et al., 1991	X		X	X	X	
Peloquin et al., 2004	X		X	X	X	
Rodriguez-Noriega et al., 1995	X		X		X	
Viscoli et al., 1991	X		X	X	X	

[a]The full spellout of this group's name is The International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer.

Study Quality and Participant Characteristics

The methodological quality of the 11 controlled trials and four case series are reported in Table 2. The agreement between two independent quality raters was 90%. Quality appraisal scores ranged from two to six out of six possible areas. Half of the studies (53%) met at least four out of six quality markers. Only one study (Kotze, Bartel, & Sommers, 1999) met all quality appraisal points. The majority of studies (80%) fell short in the blinding of assessors. Additionally, many of the studies did not report hearing status pre-treatment, define hearing outcome measures used, or provide adequate follow-up of participants at post-treatment.

Table 2 provides the detailed characteristics of the 1,127 participants studied. (Fausti et al. [1999] is not included in these counts, as the incidence of hearing loss was reported by ear and not by participant.) Of these participants, the majority (58%) were treated with amikacin for bacterial infections, and 36% were cancer patients. Other medical diagnoses included pelvic inflammatory disease and tuberculosis. Medical diagnosis was not reported in two studies.

Of the 15 included studies, five examined the impact on hearing after amikacin treatment, specifically in the pediatric population (< 1 day to 17 years), and five did so in the adult population. The remaining studies included both children and adults.

Beyond age and gender (cumulative 57% male subjects, 43% female subjects), very little demographic, social, or cultural data were reported, making it difficult to assess the generalizability of these findings to diverse populations. One study (Blum, 1995) reported that 89% of subjects were White, but no other studies provided data on race or other social or cultural data. The studies themselves were conducted in a broad range of geographical settings. Three of the studies were conducted through multisite, multinational consortia; two studies had sites in Belgium, South Africa, Sweden, and the United States; and one study had sites in Greece, Holland, Italy, and Mexico.

Table 2 Methodological quality and patient characteristics of 15 included studies.

Study	Study design	Medical diagnosis	Mean age yrs (range)	Sample clearly defined	Pre-hearing status reported	> 80% follow up	Outcome measure(s) clearly defined	Assessor blinded	Same treatment regime or stratified	Quality score
Axdorph et al., 1993	Case series	Cancer	59 (16–84)	Y	N	Y	Y	N	Y	4/6
Blum, 1995	Trial	Bacterial infection	53	Y	N	N	Y	N	Y	3/6
The International Antimicrobial Therapy Cooperative Group, 1993[a]	Trial	Cancer	29 (1–84)	Y	N	N	Y	Y	Y	4/6
Charnas et al., 1997	Trial	Cancer	6 (median) (1–17)	Y	N	N	Y	N	Y	3/6
de Jager & van Altena, 2002	Case series	Tuberculosis (bacterial infection)	38 (10–83)	Y	N	N	Y	N	N	2/6
Fausti et al., 1999	Case series	NR	NR	N	Y	Y	Y	N	N	3/6
Forsyth et al., 1997	Trial	Bacterial infection	8 (< 1–12)	Y	N	N	N	Y	Y	3/6
Giamarellou et al., 1991	Trial	Bacterial infection	57 (20–81)	Y	N	Y	Y	N	Y	4/6
Ibrahim et al., 1990	Trial	Pelvic inflammatory disease (bacterial infection)	(7–43)	Y	N	Y	Y	N	Y	4/6

(continued)

Table 2 (continued)

Study	Study design	Medical diagnosis	*M* (range)	Sample clearly defined	Pre-hearing status reported	> 80% follow up	Outcome measure(s) clearly defined	Assessor blinded	Same treatment regime or stratified	Quality score
Kotze et al., 1999	Trial	Bacterial infection	< 1	Y	Y	Y	Y	Y	Y	6/6
Langhendries et al., 1993	Trial	NR	< 1	Y	N	Y	Y	N	Y	4/6
Maller et al., 1991	Trial	Bacterial infection	64	Y	Y	N	Y	N	N	3/6
Peloquin et al., 2004	Trial	Bacterial infection	50 (27–75)	Y	Y	Y	Y	N	Y	5/6
Rodriguez-Noriega et al., 1995	Trial	Bacterial infection	(18–87)	Y	N	N	Y	N	Y	3/6
Viscoli et al., 1991	Case series	Cancer	3 (*Med.*) (2–13)	Y	Y	N	Y	N	Y	4/6

Note. M = mean age in years; Med. = median; NR = not reported.

[a]The full spellout of this group's name is The International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer.

Clinical Question 1: What Is the Likelihood of Persons Treated With Amikacin Developing Hearing Loss?

All but two studies (Forsyth, Botha, & Hadley, 1997; Langhendries et al., 1993) provided data to address the likelihood of hearing loss after amikacin treatment (see Table 3). Incidence of hearing loss reported ranged from 0% to 55%. One study, Fausti et al. (1999), reported hearing loss by ear with an incidence of 33%. Objective hearing instrumentation included pure-tone audiometry (PTA) and brainstem auditory-evoked potentials (BAEP). One study (Axdorph et al., 1993) also assessed hearing using patient self-report. Criteria used in determining presence or absence of hearing loss varied across studies.

Previous studies have indicated that drug-induced hearing loss is more frequently observed at high frequencies (Munckhof, Grayson, & Turnidge, 1996). Two studies (Fausti, et al., 1999; Ibrahim et al., 1990) included in this review tested for high-frequency (> 8 kHz) hearing loss. Ibrahim et al. (1990) found that the majority of individuals exhibiting hearing loss (70%) did so in the high-frequency range (10–18 kHz). Fausti et al. (1999) reported a total incidence of 33% by ear for individuals treated with amikacin. Unfortunately, Fausti et al. did not present drug-specific hearing loss data by frequency, and incidence of high-frequency hearing loss is not known. Axdorph et al. (1993) did not complete high-frequency testing; however, they did separate the results of patients with higher frequency loss (3–8 kHz) within the standard frequencies (0.25–8 kHz). Results of Axdorph et al. (1993) indicate that the majority (70%) of individuals with hearing loss experienced hearing loss above 3 kHz.

Table 3.
Studies addressing incidence of hearing loss post amikacin treatment (question 1).

Study	Assessment instrument			HL criteria (dB loss post-treatment)	% HL post-treatment
	Subjective	PTA	BAEP		
Axdorph et al., 1993	X	X		patient self-report ≥ 15 dB 1 freq/1 ear *or* ≥ 10 dB 3 freq/1 ear	13% (5/39)(subj.) 51% (20/39)(PTA)
Blum, 1995		X		≥ 20 dB 2 freq	3% (9/349)
The International Antimicrobial Therapy Cooperative Group, 1993[a]		X		≥ 20 dB 1 freq/1 ear	8% (11/144)
Charnas et al., 1997		X		≥ 20 dB 1 freq	1% (3/213)

(continued)

Table 3 (continued)

Study	Assessment instrument			HL criteria (dB loss post-treatment)	% HL post-treatment
	Subjective	PTA	BAEP		
de Jager & van Altena, 2002		X		≥ 15 dB 2 freq or ≥ 20 dB 1 freq	13% (1/8)
Fausti et al., 1999		X		≥ 20 dB 1 freq or ≥ 10 dB 2 freq or Loss of response 3 freq	33% (13/39) (by ear)
Giamarellou et al., 1991		X		≥ 15 dB 2 freq	3% (2/60)
Ibrahim et al., 1990		X		≥ 15 dB 1 freq/1 ear	25% (10/40)
Kotze et al., 1999			X	Peak V ≥ 57 dB peSPL at stimulation rate of 50 clicks	0% (0/32)
Maller et al., 1991		X		≥ 15 dB 2 freq	1% (1/105)
Peloquin et al., 2004		X		≥ 20 dB 1 freq/1 ear	55% (12/22)
Rodriguez-Noriega et al., 1995		X		≥ 20 dB 2 freq/1 ear	0% (0/43)
Viscoli et al., 1991		X		≥ 20 dB 1 freq/1 ear	10% (1/10)

Note. PTA = pure-tone audiometry; BAEP = brainstem auditory-evoked potentials; dB = decibel; peSPL= peak equivalent sound pressure level; freq = frequency; subj. = subject; freq = frequency.

[a]The full spellout of this group's name is The International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer.

Because of the heterogeneity of the included studies, particularly differences in hearing loss criteria used across studies, a reliable calculation of the pooled incidence of hearing loss could not be completed. In addition, factors such as medical diagnosis, age, methodological quality, and study design contribute to the variability among the included studies. Given this, the results of this question are further stratified in order to note trends among these factors. Because Fausti et al. (1999) analyzed results by ear rather than by individual, their results are not included in these analyses.

Hearing loss criteria

The specificity of the criteria used to define hearing loss in the studies varied from a low of 10 dB to a high of 20 dB. In addition, some criteria required hearing loss at only one frequency, whereas others required two or even three adjacent frequencies. The Rodriguez-Noriega et al. (1995) and Blum (1995) studies utilized the most specific criteria, a loss of at least 20 dB in at least two adjacent frequencies. These studies with specific criteria reported incidences of 0% and 3%. At the other end of the spectrum, the Axdorph et al. (1993) and Ibrahim et al. (1990) studies used the most sensitive criteria, setting the threshold lower and requiring losses at only a single frequency. Those two studies reported much higher incidence, ranging from 25% to 51%.

A trend was apparent in the selection of which criteria to use. In the six studies published prior to 1995, only two of the six utilized the criterion of at least a 20-dB hearing loss. In studies published in 1995 or later, all six set the threshold of at least 20 dB.

Medical diagnosis

As noted in Table 2, four of the studies involved cancer patients, and eight included patients with bacterial infections. The four cancer studies reported incidence ranging from 1% to 51%. The eight infectious disease studies reported incidence of hearing loss ranging from 0% to 55%.

Age

Three studies included only children, whereas five were limited to adults. The pediatric studies (Charnas, Luthi, & Ruch, 1997; Kotze, Bartel, & Sommers, 1999; Viscoli et al., 1991) reported incidence ranging from 0% to 10%. The adult studies (Blum, 1995; Giamarellou et al., 1991; Maller, Ahrne, Eilard, Eriksson, & Lausen, 1991; Peloquin et al., 2004; Rodriguez-Noriega et al., 1995) reported incidence ranging from 0% to 55%.

Study design

As reported in Table 2, nine of the studies were controlled trials, and the remaining three were case series. Incidence reported from the trials ranged from 0% to 55%. Incidence from the case series ranged from 10% to 51%.

Methodological quality

Incidence reported from the seven studies that were scored as a four or higher out of the six quality criteria ranged from 0% to 55%. In studies scored as a three or lower, the incidence ranged from 0% to 13%.

Clinical Question 2: What Is the Persistence of Hearing Loss in Persons Treated With Amikacin?

Only three studies (Axdorph et al., 1993; Forsyth et al., 1997; Kotze et al., 1999) provided data to address persistence of hearing loss in persons treated with amikacin. Axdorph et al. (1993) reported follow up hearing outcomes on 20% of the participants with identified hearing loss. Three of the four participants (75%) demonstrated continued hearing loss at two month follow up. Forsyth et al. (1997) reported follow up on 13 of 14 individuals with identified hearing loss. Although the authors reported 69% (9/13) with persistent hearing loss, length of follow was not reported. Kotze et al. (1999) was the only study to examine the long term incidence of hearing loss in participants regardless of hearing status post amikacin treatment. While no participant experienced a loss of hearing immediately post-treatment, 4% (1/26) developed hearing loss on subsequent pure tone audiometry. However, time of follow- up was not reported.

Clinical Question 3: Is the Likelihood of Amikacin-Induced Hearing Loss Affected by Dosage?

Thirteen studies provided data to address the effect of amikacin dosage on hearing loss. Tables 4 and 5 report incidence of hearing loss by daily dosage (mg/kg of body weight per day). Incidence of hearing loss in participants who received 14–15mg/kg a day of amikacin ranged from 0% to 64%, and for those who received 20mg/kg a day ranged from 3% to 10% post-treatment.

Table 4. *Incidence of HL by dosage: 14–15mg/kg of body weight/day.*

Study	*N*	% HL
Axdorph et al., 1993	14/39	51
Blum, 1995	9/349	3
Forsyth et al., 1997	14/40	35
Giamarellou et al., 1991	2/60	3
Ibrahim et al., 1990	10/40	25
Kotze et al., 1999	0/32	0
Langhendries et al., 1993	0/22	0
Maller et al., 1991	1/105	1
Peloquin et al., 2004	7/11	64
Rodriguez-Noriega et al., 1995	0/43	0

Table 5. *Incidence of HL by dosage: 20mg/kg of body weight/day.*

Study	*N*	% HL
The International Antimicrobial Therapy Cooperative Group, 1993[a]	11/144	8
Charnas et al., 1997	3/113	3
Viscoli et al., 1991	1/10	10

[a]The full spellout of this group's name is The International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer.

Clinical Question 4: Is the Likelihood of Amikacin-Induced Hearing Loss Affected by Route of Administration?

No comparative studies examined incidence of hearing loss by route of administration such as topical, oral, or intravenous (IV) therapy. Of the 13 studies that reported administration route, all provided amikacin via IV, with one study (Rodriguez-Noriega et al.,1995) also utilizing intramuscular (IM) administration. However, findings from this study were not separated by route of administration (IV vs. IM). Therefore, no conclusions could be drawn.

Clinical Question 5: Is the Likelihood of Amikacin-Related Hearing Loss Affected by Administration Schedule?

Twelve studies provided information to address the effect of administration schedule on the likelihood of amikacin-induced–related hearing loss (see Table 6). Eight studies examined once-daily administration of amikacin. The percentage of hearing loss post amikacin treatment for this group ranged from 0% to 20%. Eight studies provided amikacin treatment twice daily. The incidence of hearing loss for this group ranged from 0% to 55%. Two studies examined the effects of three times–daily administration. One study (The International Antimicrobial Therapy Cooperative Group ,1993) reported an incidence of 7%, whereas the other (Charnas et al., 1997) reported an incidence of 1%.

Table 6. *Incidence of amikacin-induced hearing loss (HL) by schedule.*

Study	mg/kg per body weight	*N*	% HL post-treatment
Studies with weekly administration			
Peloquin et al., 2004	25 mg/kg—3×/wk	5/11	45%
Peloquin et al., 2004	15 mg/kg—5×/wk	7/11	64%
Studies with once-daily administration			
The International Antimicrobial Therapy Cooperative Group, 1993[a]	20	6/70	9%
Charnas et al., 1997	20	2/109	2%
Forsyth et al., 1997	15	3/20	15%
Giamarellou et al., 1991	15	1/30	3%
Ibrahim et al., 1990	14	4/20	20%
Langhendries et al., 1993	15	0/10	0%
Maller et al., 1991	15	1/54	2%
Viscoli et al., 1991	20	1/10	10%
Studies with twice-daily administration			
Axdorph et al., 1993	7.5	20/39	51%
Blum, 1995	7.5	9/349	3%
Rodriguez-Noriega et al., 1995	7.5	0/43	0%
Forsyth et al., 1997	7.5	11/20	55%
Giamarellou et al., 1991	7.5	1/30	3%
Ibrahim et al., 1990	7	6/20	30%
Langhendries et al., 1993	7.5	0/12	0%
Maller et al., 1991	7.5	0/51	0%
Studies with three times–daily administration			
The International Antimicrobial Therapy Cooperative Group, 1993[a]	6.5	5/74	7%
Charnas et al., 1997	6.5	1/104	1%

[a]The full spellout of this group's name is The International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer.

Eight of the included studies explored a direct comparison of two amikacin treatment schedules (see Table 7). Seven of the eight studies found no statistically significant differences between groups, whereas one study (Forsyth et al., 1997) reported a statistically significant increase (p = .02) in hearing loss with twice-daily, as compared with once-daily, administration (0.25 kHz and 6 kHz, respectively). Forsyth et al. (1997) noted that limitations of the study, including a lack of data on baseline hearing status and challenges in assessing young children because of shortened attention spans, may have impacted the results. Also, the lack of statistically significant differences at high frequencies (6–8 kHz) lead the study authors to question if the hearing effects are actually drug-induced (as most drug-induced hearing losses occur in the high frequencies; Forsyth et al., 1997, p. 258).

Table 7. *Studies comparing amikicin schedules and hearing loss.*

	Doses per week					
Study	**OD**	**BD**	**TD**	**3×/wk**	**5×/wk**	***p* (significance)**
The International Antimicrobial Therapy Cooperative Group, 1993[a]	9% (6/70)		7% (5/74)			p = .76
Charnas et al., 1997	2% (2/109)		1% (1/104)			p = 1.0
Forsyth et al., 1997	15% (3/20)	55% (11/20)				p = .02*
Giamarellou et al., 1991	3% (1/30)	3% (1/30)				p = 1.0
Ibrahim et al., 1990	20% (4/20)	30% (6/20)				p = .72
Langhendries et al., 1993	0% (0/10)	0% (0/12)				p = 1.0
Maller et al., 1991	2% (1/54)	0% (0/51)				p = 1.0
Peloquin et al., 2004				45% (5/11)	64% (7/11)	p = .67

Note. OD =once daily; BD = twice daily; TD = three times daily; * = statistically significant.

[a]The full spellout of this group's name is The International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer.

Clinical Question 6: Is There Evidence of a Synergistic Effect on Hearing Loss if Multiple Ototoxic Drugs (e.g., Aminoglycosides, Antineoplastics, etc.) Are Taken Concomitantly With Amikacin?

Two studies examined the possible synergistic effects of multiple ototoxic drugs that are concurrently administered. The Axdorph et al. (1993) study involved 52 patients receiving amikacin, 26 of whom were also receiving vancomycin. Although data on hearing loss were not presented separately for the two groups, the authors cited concomitant vancomycin administration as "among the factors found not to be statistically significantly associated with development of hearing loss" (p. 405). The de Jager and van Altena (2002) study involved two patients who received amikacin and six others who, in addition to receiving amikacin, also received kanamycin and/or streptomycin. One of the two patients who received only amikacin experienced hearing loss post-treatment. There were no occurrences of hearing loss among the patients who received amikacin in combination with kanamycin and/or streptomycin.

Discussion

This systematic review was intended to provide additional insight into the likelihood of individuals developing hearing loss as a result of amikacin administration. Further, the effect of differing dosage regimens, schedules of administration, routes of administration, and concurrent drug use were investigated to determine potential effects on hearing. All follow-up information was extracted from studies in order to assess the persistence of hearing loss and/or latency of hearing loss symptoms. Unfortunately, few studies were available to address several of these clinical questions, and the heterogeneity of the studies prevented pooling of incidence data necessary to draw strong conclusions.

The incidence of hearing loss post-amikacin treatment ranged from 0% to 55% across the studies included in this review. This range is larger than the range reported in a previous systematic review (1.2%–20%) published in 1995 (Blaser & König). These discrepancies may be explained by the larger number and the more recent studies included in the present systematic review. Two of the higher incidences of hearing loss reported in this study were demonstrated by studies published after 1995. Analysis of hearing loss incidence by medical diagnosis, age, study design, and methodological quality yielded no apparent trends.

Differences in the frequencies of hearing tested and differences in the criteria for consideration of hearing loss may have significantly impacted the findings of this review. One study (Ibrahim et al., 1990) reported that the majority (70%) of participants experienced hearing loss above 10 kHz. As the majority of studies did not test hearing above 8 kHz, any individuals in these studies with hearing loss at frequencies above 8

kHz would not have been reported. The lack of high-frequency hearing loss testing could lead to significant underestimation of hearing loss in patients treated with amikacin. Differences across studies in the criteria used to define the presence or absence of hearing loss could also impact the findings from this review. Studies using the most sensitive criteria to define hearing loss reported incidences ranging from 25% to 51%, whereas studies utilizing very specific criteria reported hearing loss ranging from 0% to 3%. These differences in hearing loss criteria alone could account for the wide variability of hearing loss incidence post-amikacin treatment noted across studies.

Regarding the persistence or latency of hearing loss at follow-up after amikacin treatment, only three studies provided data to address this question. The hearing loss of several participants in the studies improved or worsened over an unknown period of time following amikacin treatment. Additional research is needed to determine the number of individuals who exhibit hearing changes after treatment has been completed and the length of time over which these changes occur. This research should address individuals with and without hearing loss post-treatment to accurately document latent drug effects.

No apparent trends in incidence were noted across varying dosages administered, and no studies undertook comparisons of different dosage levels. Similarly, conclusions cannot be drawn regarding the effect of route of administration on hearing loss. The majority of studies administered amikacin intravenously. No analyzable data was obtained to determine incidence of hearing loss by any other means. The findings related to amikacin dosing schedules are consistent with the previous systematic review conducted in 1995 by Blaser and Konig, which calculated no pooled difference in hearing loss incidence between once- and multiple-daily dosing of amikacin. Two studies investigated the effect of amikacin administration concomitantly with other potentially ototoxic drugs. Concurrent administration of vancomycin, kanamycin, and/or streptomycin did not significantly increase the incidence of hearing loss in patients receiving amikacin. However, these findings must be interpreted cautiously given the limited amount of research available on this topic.

Future research in this topic area should include comparative studies of dosage and route-of-administration effects on the incidence of hearing loss and should follow participants for a pre-defined time period post-treatment to document changes in hearing. Additional research is also needed regarding the effects of concurrent drug administration, especially with drugs that are potentially ototoxic. Audiologic measures should include high-frequency testing, and efforts should be made to increase the consistency of criteria used to define hearing loss. In the absence of such criteria, researchers should consider making raw data available in order to increase analyzability across studies.

The findings from these studies do not provide substantial help for clinicians concerned about the potential for hearing loss in patients receiving amikacin. There are, as yet, no well-documented risk factors that can be used to differentiate higher- from lower-risk groups. Until more high-quality, experimental studies—using standardized case definitions—are completed, clinical decision making related to initiating, modifying, or terminating amikacin therapy will be largely or entirely left up to the expertise and judgment of the clinician and the patient's tolerance for risk of hearing loss relative to negative sequelae from the condition being treated.

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